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EXAMINER	
BRISTOL, LYNN ANNE	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,795	NAKANO ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *19,20 and 24-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,21-23 and 28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 June 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-33 are all the pending claims for this application.

Election/Restrictions

2. Applicant's election without traverse of Group I (Claims 1-18, 21-23 and 28-33) in the reply filed on 1/18/08 is acknowledged.

3. Claims 19, 20 and 24-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/18/08.

4. Claims 1-18, 21-23 and 28-33 are all the pending claims under examination.

Information Disclosure Statement

5. The references cited in the IDS of 12/10/08 have been considered and entered. The examiner's initialed copy of the 1449 form is attached.

Drawings

6. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because each the drawing sheets for Figures 20 contains Japanese language characters. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office

action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Specification

7. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See p. 124, line 5. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

8. Claim 28 is objected to for an apparent typographical error. The claim fails to include the term "or" between elements (14) and (15) to indicate any one of the alternatives of (1) –(15).

9. Claim 15 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 15 is drawn to the antibody of Claim 9 "which is a humanized antibody." Claim 9 is drawn to a humanized antibody capable of binding to glypican 3. Claim 15 recites the same subject matter as Claim 9.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claims 1-6, 10-14, 16-18 and 28-33 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-6, 10-14, 16-18 and 28-33 are directed to an antibody. The claims read on any antibody that is found in nature. Products of nature do not constitute patentable subject matter as defined in 35 USC 101. See MPEP 2105. Since an antibody does not exist in nature in purified form, it is suggested that Applicant use the language "isolated" or "purified" in connection with the antibody to identify a product that is not found in

nature.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 17, 18 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 17 is indefinite for the recitation “has a high CDC activity” because the term “high” is a relative term which renders the claim indefinite. The term "high" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. What is a standard reference comparison against which the antibody CDC activity can be determined to be high versus low, for example?

Claim 18 is similarly rejected for the recitation “has a high ADCC activity” for the use of the term “high.”

b) Claim 30 is indefinite for the recitation “selected from” because if the intended meaning is for a Markush group, then the Markush group language is improper. See MPEP 803.02.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement (1)

12. Claims 1, 2, 4, 5, 7, 8, 21-23 and 28-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

the monoclonal anti-glypican 3 antibodies: **GC33** (VH CDRs SEQ ID NOS: 123, 124 and 125, and VL CDRs SEQ ID NOS: 143, 144 and 158); **M11F1** (VH CDRs SEQ ID NOS: 109, 110 and 111, and VL CDRs SEQ ID NOS: 143, 144 and 145); **M3B8** (VH CDRs SEQ ID NOS: 106, 107 and 108, and VL CDRs SEQ ID NOS: 140, 141 and 142); **GC199** (VH CDRs SEQ ID NOS:132, 133 and 134, and VL CDRs SEQ ID NOS: 167, 168 and 169); **GC202** (VH CDRs SEQ ID NOS:106, 135 and 136, and VL CDRs SEQ ID NOS: 170, 144 and 171); **GC179** (VH CDRs SEQ ID NOS: 126, 127 and 128, and VL CDRs SEQ ID NOS: 159, 160 and 161); **GC194(1)** (VH CDRs SEQ ID NOS: 129, 130 and 131, and VL CDRs SEQ ID NOS: 162, 147 and 163); **GC194(2)** (VH CDRs SEQ ID NOS: 129, 130 and 131, and VL CDRs SEQ ID NOS: 164, 165 and 166); **M13B3** (VH CDRs SEQ ID NOS: 103, 104 and 105, and VL CDRs SEQ ID NOS: 137, 138 and 139); **L9G11** (VH CDRs SEQ ID NOS: 118, 121 and 122, and VL CDRs SEQ ID NOS: 155, 156 and 157); **M6B1** (VH CDRs SEQ ID NOS: 115, 116 and 117, and VL CDRs SEQ ID NOS: 149, 150 and 151); **M5B9** (VH CDRs SEQ ID NOS: 112, 113 and 114, and VL CDRs SEQ ID NOS: 146, 147 and 148); and **M10D2** (VH CDRs SEQ ID NOS: 118, 119 and 120, and VL CDRs SEQ ID NOS: 152, 153 and 154); and

humanized versions of the GC33 monoclonal comprising a VH region of SEQ ID NO: 84, 85, 86, 87, 88, 89, or 90 paired with a VL of SEQ ID NO: 92; and

modified, humanized GC33 L chains comprising SEQ ID NO: 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204 or 205 paired with humanized, GC33 H chain of ver. k (SEQ ID NO:90),

does not reasonably provide enablement for an anti-glypican 3 antibody comprising a single variable domain (i.e., VH or VL only); or mixing VL CDRs from a given parent anti-glypican 3 antibody with another anti-glypican 3 antibody and/or mixing VH CDRs from a given parent anti-glypican 3 antibody with another anti-glypican 3 antibody; or mixing any light chain or VL domain from a given parent anti-glypican 3 antibody with any heavy chain or VH domain from another anti-glypican 3 antibody; or any of the anti-glypican 3 antibodies (e.g., GC33, M11F1, M3B8, GC199, GC202, GC179, GC194(2), M13B3, L9G11, M6B1, M5B9, M10D2) comprising any amino acid substitution, deletion, addition or insertion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir.1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention/ Skill in the Art

The claims are interpreted as being drawn to an antibody comprising a VH region having the following CDRs: (1) VH CDRs SEQ ID NOS: 123, 124 and 125 (**GC33),** (2) VH CDRs SEQ ID NOS: 109, 110 and 111 (**M11F1)**, (3) VH CDRs SEQ ID NOS: 106, 107 and 108 **M3B8**, (4) VH CDRs SEQ ID NOS:132, 133 and 134 (**GC199),** (5) VH CDRs SEQ ID NOS:106, 135 and 136 (**GC202)**, (6) VH CDRs SEQ ID NOS: 126, 127 and 128 (**GC179)**, (7) VH CDRs SEQ ID NOS: 129, 130 and 131 (**GC194(1)**), (8) VH CDRs SEQ ID NOS: 103, 104 and 105 (**M13B3**), (9) VH CDRs SEQ ID NOS: 118, 121 and 122 (**L9G11**), (10) VH CDRs SEQ ID NOS: 115, 116 and 117 (**M6B1),** (11) VH CDRs SEQ ID NOS: 112, 113 and 114 (**M5B9**), and VH CDRs SEQ ID NOS: 118, 119 and 120 (**M10D2**) (Claim 1), or

an antibody comprising a VL region having the following CDRs: (1) VL CDRs SEQ ID NOS: 143, 144 and 158 (**GC33),** (2) VL CDRs SEQ ID NOS: 143, 144 and 145 (**M11F1)**, (3) VL CDRs SEQ ID NOS: 140, 141 and 142 (**M3B8)**, (4) VL CDRs SEQ ID NOS: 167, 168 and 169 (**GC199),** (5) VL CDRs SEQ ID NOS: 170, 144 and 171 (**GC202)**, (6) VL CDRs SEQ ID NOS: 159, 160 and 161 (**GC179)**, (7) VL CDRs SEQ ID NOS: 162, 147, 163 **GC194(2)**, (8) VL CDRs SEQ ID NOS: 164, 165, 166 (**GC194(2)**), (9) VL CDRs SEQ ID NOS: 137, 138, 139 (**M13B3**), (10) VL CDRs SEQ ID NOS: 155, 156, 157 (**L9G11**), (11) VL CDRs SEQ ID NOS: 149, 150, 151 (**M6B1**), (12) VL CDRs SEQ ID NOS: 146, 147, 148 (**M5B9**), or (13) VL CDRs SEQ ID NOS: 152, 153, 154 (**M10D2**) (Claim 2), or

an antibody comprising a VH of SEQ ID NO: 84, 85, 86, 97, 88, 89 or 90 (Claim 4), or and antibody having a LV of SEQ ID NO: 92 (Claim 5), or a humanized antibody

of Claims 1-6 (Claim 7), or an antibody having an activity equivalent to the antibody of Claim 7 having one or more amino acid substitutions, deletions, additions or insertions (claim 8), or a cell growth inhibitor comprising the antibody of Claim 7 (Claim 21), or an anti-cancer agent comprising the antibody of Claim 7 (Claim 22) for treating a hepatoma (Claim 23), or an antibody comprising a VL region having a CDR1 of SEQ ID NO: 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187 or 188, a CDR 2 of SEQ ID NO: 144 and a CDR3 of SEQ ID NO:158 (Claim 28), or an antibody comprising a VH region comprising CDR 1-3 of SEQ ID NOS: 123, 124 and 125, respectively, paired with a VL region comprising a CDR1 of SEQ ID NO: 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187 or 188, a CDR 2 of SEQ ID NO: 144 and a CDR3 of SEQ ID NO:158 (Claim 29), or an antibody comprising any VL region of SEQ ID NO: 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204 and 205 (Claim 31), or an antibody comprising any VL region of SEQ ID NO: 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204 and 205 paired with any VH region of SEQ ID NO: 84, 85, 86, 87, 88, 89 or 90 (Claim 31), or a human antibody of Claims 28-31 (Claim 32).

The relative skill in the art required to practice the invention is a molecular immunologist with a background in antibody biochemistry.

Disclosure in the Specification

The specification is enabling for producing hybridomas against glypican 3 protein and screening for the monoclonal anti-glypican 3 antibodies: **GC33** (VH CDRs SEQ ID NOS: 123, 124 and 125, and VL CDRs SEQ ID NOS: 143, 144 and 158); **M11F1** (VH

CDRs SEQ ID NOS: 109, 110 and 111, and VL CDRs SEQ ID NOS: 143, 144 and 145); **M3B8** (VH CDRs SEQ ID NOS: 106, 107 and 108, and VL CDRs SEQ ID NOS: 140, 141 and 142); **GC199** (VH CDRs SEQ ID NOS:132, 133 and 134, and VL CDRs SEQ ID NOS: 167, 168 and 169); **GC202** (VH CDRs SEQ ID NOS:106, 135 and 136, and VL CDRs SEQ ID NOS: 170, 144 and 171); **GC179** (VH CDRs SEQ ID NOS: 126, 127 and 128, and VL CDRs SEQ ID NOS: 159, 160 and 161); **GC194(1)** (VH CDRs SEQ ID NOS: 129, 130 and 131, and VL CDRs SEQ ID NOS: 162, 147 and 163); **GC194(2)** (VH CDRs SEQ ID NOS: 129, 130 and 131, and VL CDRs SEQ ID NOS: 164, 165 and 166); **M13B3** (VH CDRs SEQ ID NOS: 103, 104 and 105, and VL CDRs SEQ ID NOS: 137, 138 and 139); **L9G11** (VH CDRs SEQ ID NOS: 118, 121 and 122, and VL CDRs SEQ ID NOS: 155, 156 and 157); **M6B1** (VH CDRs SEQ ID NOS: 115, 116 and 117, and VL CDRs SEQ ID NOS: 149, 150 and 151); **M5B9** (VH CDRs SEQ ID NOS: 112, 113 and 114, and VL CDRs SEQ ID NOS: 146, 147 and 148); and **M10D2** (VH CDRs SEQ ID NOS: 118, 119 and 120, and VL CDRs SEQ ID NOS: 152, 153 and 154) (Examples 6-9, 13, 18); and

humanized versions of the GC33 monoclonal comprising a VH region of SEQ ID NO: 84, 85, 86, 87, 88, 89, or 90 paired with a VL of SEQ ID NO: 92 (Example 24); and

modified, humanized GC33 L chains comprising SEQ ID NO: 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204 or 205 paired with humanized, GC33 H chain of ver. k (SEQ ID NO:90) (Example 25).

The specification is not enabling for the antibodies encompassed by the scope of the claims including anti-glypican antibodies comprising a single VH or a single VL

domain, or mixing VL CDRs from a given parent anti-glypican 3 antibody with another anti-glypican 3 antibody and/or mixing VH CDRs from a given parent anti-glypican 3 antibody with another anti-glypican 3 antibody; or mixing any light chain or VL domain from a given parent anti-glypican 3 antibody with any heavy chain or VH domain from another anti-glypican 3 antibody; or any of the anti-glypican 3 antibodies (e.g., GC33, M11F1, M3B8, GC199, GC202, GC179, GC194(2), M13B3, L9G11, M6B1, M5B9, M10D2) comprising any amino acid substitution, deletion, addition or insertion.

The claims are not commensurate in scope with the enablement provided in the specification. The specification does not support the broad scope of the claims which encompass modifications to the amino acid sequence of the antibody because the specification does not disclose the following:

The general tolerance to modification and extent of such tolerance;

The specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; and

The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed anti-glypican antibodies in manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

Without such guidance, the changes which can be made in the antibodies structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

Prior Art Status: Single Variable Domain Antibodies

Selecting and producing just any variable domain substituted antibody with the ability to properly associate and assemble into a fully functional antibody which maintains the binding specificity for the original antigen would be highly unpredictable based on the methods described in the specification and the prior art disclosures.

Smith-Gill et al. (J. Immunol. 139:4135-4144 (1987)) observed from chain recombination experiments that through interactions between the VH/VL pair, specificity for antigen is H chain determined, specific binding is increased when L chains of the same parental isotype are used, and that both H and L chains determine fine specificity.

Kumar et al. (J. Biol. Chem. 275:35129-35136 (2000)) discloses Fab molecules with anti-DNA (light chain) and anti-cardiolipin (heavy chain) binding activities, and that pairing of the partner chains is dependent on the particular H/L chain pairing.

Song et al. (Biochem Biophys Res Comm 268:390-394 (2000)) discloses that affinity and specificity of scFv for preS1 protein of HBV is dependent on S-S bond formation in conferring correct refolding of the fragments for retaining binding properties, and that L chains are predominant in antigen binding.

Prior Art Status: CDR-domain Modifications

The claims encompass antibodies comprising mixing CDR domains from different chains and possibly even different anti-glypican 3 antibodies. The claims encompass any amino acid substitution, deletion, addition and/or insertion to any region of the antibody. Applicants have not shown that any antibody comprising less than a full complement of VH CDR 1-3 and VL CDR 1-3 from a given parent anti-glypican 3 antibody would retain the antigen binding for glypican 3. In fact there are numerous publications acknowledging that the conformation of CDRs as well as framework regions (FR) influence binding.

MacCallum *et al.* (J. Mol. Biol. (1996) 262:732-745) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.).

Pascalis *et al.* (Journal of Immunology (2002) 169, 3076-3084) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset *et al.* ((2003) BBRC 307, 198-205), which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset *et al.* also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and a framework residue located just before the H3 (see page 202, left col.).

Vajdos *et al.* ((2002) J. Mol. Biol. 320, 415-428) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.).

Holm *et al* ((2007) Mol. Immunol. 44: 1075-1084) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract).

Chen *et al.* (J. Mol. Bio. (1999) 293, 865-881) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866).

Wu *et al.* J. Mol. Biol. ((1999) 294, 151-162) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Thus, while one can make the statement that a single CDR makes a significant contribution in the antigen binding, the residues in these CDRs are not the only residues that influence binding and in fact the prior art as well as applicants own disclosure do not support that it was clearly established, that the a single CDR domain alone is sufficient to define the binding specificity of an antibody, and that multiple antibodies can predictably be generated having the same binding specificity based on a single CDR (or less than full complement of VH and VL CDRs).

Analyzing applicants own disclosure, which while it does have divergent CDR residues, the majority of these heavy chain CDRs were paired with specific light chain CDRs. Additionally, the data seem to indicate that it is the frameworks and CDRs that contribute to antigen binding. Further, there are no working examples of mixing or matching of the light chain CDRs or heavy chain CDRs in just any framework and producing an anti-glypican 3 antibody that binds antigen as broadly claimed or suggested.

Prior Art Status: Conservative Amino Acid Substitutions within CDR/FR Residues

The claims encompass antibodies comprising VH domains, VL domains and CRDs comprising amino acid substitutions, deletions, additions and insertions. It is not well established in the art that all variable domains are amenable to any modifications much less even conservative modifications. Numerous publications acknowledge that even conservative substitutions would in fact change the binding ability of antibodies if not substantially reduce the affinity.

Brummell *et al*. (Biochemistry 32:1180-1187 (1993)) found that mutagenesis of the four HCDR3 contact residues for the carbohydrate antibody (Salmomella B O-polysaccharide) in no instance improved affinity but 60% of the mutants resulted in a 10-fold drop in binding constant (affinity electrophoresis value of 0.85), while still other mutants were lower (Table 1 and p. 1183, Col. 2, ¶2 to p. 1184, Col. 1, ¶1). Brummell demonstrates that no substitution retained antigen binding affinity similar to the wild type antibody despite targeted, conservative substitutions in known contact sites.

Kobayashi *et al.* (Protein Engineering 12:879-844 (1999)) discloses that a scFv for binding a DNA oligomer containing a (6-4) photoproduct with Phe or Tyr substitutions at Trp 33 retained "a large fraction of the wild-type binding affinity, while the Ala substitution diminished antigen binding" (Table 1). However, Kobayashi notes "replacing Trp 33 with Phe or Ala alters the local environment of the (6-4) photodimer since binding is accompanied by large fluorescence increases that are not seen with the wild-type scFv" (p. 883, Col. 2, ¶3).

Burks *et al.* (PNAS 94:412-417 (1997)) discloses scanning saturation mutagenesis of the anti-digoxin scFv (26-10) which also binds digitoxin and digoxigenin with high affinity and with 42-fold lower affinity to ouabain. 114 mutant scFvs were characterized for their affinities for digoxin, digitonin, digoxignenin and oubain. Histogram analysis of the mutants (Figure 2) reveals that "not all residues are optimized in even high affinity antibodies such as 26-10, and that the absence of close contact with the hapten confers higher plasticity, i.e., the ability to tolerate a wider range of substitutions without compromising binding (p. 415, Col. 2, ¶4- p. 416, ¶1).

Although Brummell *et al*., Kobayashi *et al.* and Burks *et al.* introduced conservative amino acid substitutions into CDRs to examine binding effects these three references do not overcome the unpredictability in the art as far as demonstrating that any conservative substitution within any CDR can be made without affecting binding.

Jang *et al.* (Molec. Immunol. 35:1207-1217 (1998)) teach that single amino acid mutations to the CDRH3 of a scFV derived from 2C10, an anti-dsDNA autoantibody, reduced the binding activity about 20-50% compared to the unmutated scFv (Table 4).

Brorson *et al.* (J. Immunol. 163:6694-6701 (1999)) teach that single amino acid substitutions to the CDRs of IgM Abs for the bacterial protein, levan, are ablated.

Coleman (Research in Immunol. 145:33-36 (1994)) teaches that single amino acid changes within the interface of an antibody-antigen complex are important and that inasmuch as the interaction can tolerate amino acid sequence substitutions, "a very conservative substitution may abolish binding" while "in another, a non-conservative substitution may have very little effect on the binding" (p. 35, Col. 1, ¶1).

Unpredictability/Undue Experimentation

The specification provides no direction or guidance regarding how to produce the genus of antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Furthermore, while the level of skill required to generate the antibodies is that of a molecular biologist or molecular immunologist, the artisan of ordinary skill in the art would have been required to characterize the parent antibody, identify candidate amino acid residues for modifications in the FR and/or CDR domains, perform the mutagenesis on the FR and CDR domains, produce and express the modified antibodies, measure binding characteristics (e.g., binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (K_{off} and K_{on} respectively), and binding affinity and/or avidity compared with the parent antibody) in a BIAcore assay, and then finally perform bioassays to identify any one or more of the characteristics of an antibody. The technology to perform these experiments was available at the time of application filing, but the amount of experimentation required to generate even a single FR- and/or CDR-modified antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one or combination of all the FR and CDR modifications encompassed by the claims would result in *just any* antibody clone having retained the antigen binding activity (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in

question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Enablement (2)

13. Claims 21-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting cell growth in vitro by CDC and ADCC and in vivo in a hepatoma mouse model, does not reasonably provide enablement for using any one of the anti-glypican 3 antibodies in vivo to inhibit any kind of cell growth or to inhibit any kind of cancer much less a cancer in a human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir.1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention/ Skill in the Art

Claim 21 is drawn to a cell-growth inhibitor comprising the humanized antibody of Claim 7. Claims 22 and 23 are drawn to an anticancer agent comprising the humanized antibody of Claim 7 for treating a hepatoma.

The claims are directed to products but examined for an enabling intended use in view of the implied (Claims 21 and 22) and explicit (Claim 23) therapeutic use.

The relative skill in the art required to practice the invention is a clinician and more specifically an oncologist with a background in immunotherapeutics.

Disclosure in the Specification

Example 16 (working): 9 chimeric anti-glypican 3 antibodies were tested for CDC activity in an assay using a GP3-expressing CHO cell line (Figure 7). Of the 9, only M11F1 and M3B8 showed activity.

Example 17 (working): 9 chimeric anti-glypican 3 antibodies were tested for ADCC activity in an assay using chromium-labeled HepG2 cell line as target cells or a GP3-epxressing CHO cell line and human PBL effector cells(Figure 8). Of the 9, all showed appreciable killing of GP3-expressing CHO cells, with M3C11 and M1E7 being the highest, M11F1, M3B8, M19B11 and M18D4 being intermediate and M5B9, M10D2 and L9G11 being the lowest. Of the 9 antibodies tested on the HepG2 cell line, M3C11 and M1E7, showed the most cell killing.

Example 19 (working): the GC33 antibody was tested for ADCC activity in an assay using chromium-labeled HuH-7 cell line as target cells and mouse bone marrow effector cells(Figure 9).

Example 20 (working): the GC33 antibody was tested for its antitumor effect in a mouse model transplanted with human hepatoma cell line (Figure 10).

Thus the specification is not enabling for using any anti-glypican 3 Mab in a cell killing assay for just any cell in vitro. The specification is not enabling for using any anti-glypican 3 Mab in vivo for cell killing or growth-inhibition of any kind of tumor in any kind of animal much less a human. One skilled in the art would be required to practice undue trial and error experimentation in order to practice using the antibodies encompassed by the claims in addition to the scope of intended applications encompassed by the claims.

Prior Art Status: Treating any Cancer with an Antibody is Unpredictable

It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and drug access to tumor cells are not evenly distributed and this is an important source of heterogeneity in tumor response to drugs that does not exist in vitro. Therefore, prediction of drug effects in cancer subjects based solely on in vitro data or even limited in vivo data as in the present case is not reliable and further evaluation in animal tumor systems is essential.

Inasmuch as in vitro drug testing may be a platform technology in a determination of enablement, the complexity and difficulty of drug delivery for cancer treatment is underscored by Voskoglou-Nomikos (Clin. Can. Res. 9:4227-4239 (2003)). Voskoglou-Nomikos conducted a study using the Medline and Cancerlit databases as source material in comparing the clinical predictive value of three pre-clinical laboratory cancer models: the in vitro human cell line (Figure 1); the mouse allograft model; and

the human xenograft model (Figures 2 and 3). Significantly when each of the cancer models was analyzed against Phase II activity, there was a negative correlation for the in vitro human cell line models being predictive of good clinical value. No significant correlations between preclinical and clinical activity were observed for any of the relationships examined for the murine allograft model. And the human xenograft model showed good tumor-specific predictive value for NSCLC and ovarian cancers when panels of xenografts were used, but failed to predict clinical performance for breast and colon cancers. Voskoglou-Nomikos suggests that "the existing cancer models and parameters of activity in both the preclinical and clinical settings may have to be redesigned to fit the mode of action of novel cytostatic, antimetastatic, antiangiogenisis or immune-response modulating agents" and "New endpoints of preclinical activity are contemplated such as the demonstration that a new molecule truly hits the intended molecular target" (p.4237, Col. 1, ¶6).

Dennis (Nature 442:739-741 (2006)) also recognizes that human cancer xenograft mouse models for testing new drugs has been and will remain the industry standard or model of choice, but it is not without problems because "many more [drugs] that show positive results in mice have little or no effect in humans" (p. 740, Col. 1, ¶3). Dennis describes transgenic animal mouse models as an alternative to xenograft modeling and the general differences between mice and humans when it comes to tumor modeling: 1) cancers tend to form in different types of tissue, 2) tumors have fewer chromosomal abnormalities, 3) ends of chromosomes (telomeres) are longer, 4) telomere repairing enzyme active in cells, 5) short lifespan, 6) fewer cell divisions (10^{11})

during life than humans (10^{16}), 7) metabolic rate seven time higher than humans, and 8) lab mice are highly inbred and genetically similar. One skilled in the art would reasonably conclude that evidence obtained in mouse xenograft models would not necessarily correlate with results expected in human glypican 3-expressing tumors.

Further and as evidenced by Seaver (1994; Genetic Engineering Vol 14(14):pages 10 and 21), selection of an antibody as an immunotherapeutic agent is an unpredictable task as the antibody must possess sufficient specificity and a high degree of affinity for its target for use as an immunotherapeutic agent and because these qualities are dependent on the physiology of the particular pathology and the accessibility of the target antigen. The instant specification is silent concerning what sort of specificity and affinity would be necessary for the anti-glypican 3 antibodies so that one skilled in the art would not be able to practice the claimed invention without undue experimentation.

Therefore, due to the unpredictability of immunotherapeutics in general, and in view of the insufficient guidance and/or working examples concerning the use of the claimed antibodies as immunotherapeutic agents for inhibiting any cell growth or treating cancer in any subject, one skilled in the art would not know how to practice the broadly claimed invention, i.e., administer anti-glypican 3 antibodies for the inhibition of cell growth or the treatment of any cancer and its accompanying pathologies, including a hepatoma in any subject without undue experimentation.

Priority

14. A copy of the certified copy of the Japanese language priority document, JP 2004-2-3637, filed 7/9/04, was filed upon national stage entry for the instant application. A certified translation of the document has not been received by the Office for this application, therefore the instant claims are given a priority date for the international filing of 7/8/05. Applicants are invited to submit a translation of the Japanese priority document or a relevant portion thereof in responding to the prior art rejections.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 9-18 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Aburatani et al. (EP1411118; published 4/21/04; filed 6/21/02; cited in the IDS of 12/10/07).

Claim 9 is interpreted as being drawn to a humanized antibody capable of binding to glypican 3.

Claims 10-15 and 33 are interpreted as being drawn to an antibody capable of binding a peptide consisting of residues 524-563 of glypican 3 (Claim 10), or consisting of residues 537-563 of glypican 3 (Claim 11), or consisting of residues 550-563 of glypican 3 (Claim 12), or consisting of residues 544-553 of glypican 3 (Claim 13), or

consisting of residues 546-551 of glypican 3 (Claim 14), or the antibody of Claim 11 which does not bind to a peptide consisting of residues 550-563 of glypican 3 (Claim 33).

Claim 16 is interpreted as being drawn to an antibody that binds an epitope to which a second antibody comprising the VH CDR1-3 of SEQ ID NO: 123, 124 and 125, respectively, and the VL CDR1-3 of SEQ ID NO: 143, 144 and 158, respectively. The "second antibody" comprises the CDRs from the GC33 Mab, which as disclosed in the specification binds to an epitope in the C-terminus of GPC3.

Claims 17 and 18 are interpreted as being drawn to an antibody capable of binding to glypican 3 and having a high CDC activity (Claim 17) or a high ADCC activity (Claim 18) against a cell expressing glypican 3. Based on the teachings in the specification, for purposes of prior art, "high" activity is being interpreted as an antibody that produces any ADCC or CDC activity.

Aburatani discloses glypican 3 (GPC3) antibodies including polyclonal, monoclonal [0015] or recombinant antibodies such as chimeric or humanized antibodies [0041-0047] generated against human GPC3 or a peptide thereof [0018]. Accordingly, Aburatani reads on Claim 9 for a humanized antibody. A polyclonal antibody of Aburatani could reasonably be expected to bind any epitope falling within the structure of human GPC3 including the C-terminus. Thus it is generally expected that within a heterogeneous population of polyclonal antibodies, some could be found that would bind to a peptide consisting of residues 524-563 or residues 537-563 or residues 550-563 or residues 544 or residues 546-551 of GPC3 or that there would be an antibody

which does not bind to a peptide consisting of residues 550-563 of glypican 3. Further within the heterogeneous population of polyclonal antibodies, some could be found that could bind the same epitope as the GC33 antibody or an antibody comprising the CDRs of GC33. One would readily envisage that the antibody of Aburatani has the same properties of binding GPC3 and that humanized forms could be made therefrom. "The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1997).

Aburatani discloses a cell growth inhibitor comprising the antibodies as an active ingredient and that the antibodies also demonstrate CDC and ADCC activity [0068-0070; Figures 1 and 2]. Aburatani discloses the GPC3 Mab having ADCC and CDC activity on HuH-7 cells (Example 2).

16. Claims 10-14, 16 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Gonzalez et al. (J. Cell Biol. 141:1407-1414 (1998); cited in the IDS of 12/10/07).

The interpretation of Claims 10-14, 16 and 33 is discussed above.

Gonzalez discloses generating sheep polyclonal antibodies against a human

GPC3 fragment containing the last 70 amino acids (i.e., residues 511-580) (M & M, p. 1408, Col. 2, ¶ 7). A polyclonal antibody of Gonzalez could reasonably be expected to bind any epitope falling within the structure of the 70 amino acid residues of the C-terminal fragment of GPC3. Thus it is generally expected that within a heterogeneous population of polyclonal antibodies, some could be found that would bind to a peptide consisting of residues 524-563 or residues 537-563 or residues 550-563 or residues 544 or residues 546-551 of GPC3 or that there would be an antibody which does not bind to a peptide consisting of residues 550-563 of glypican 3. Further within the heterogeneous population of polyclonal antibodies, some could be found that could bind the same epitope as the GC33 antibody or an antibody comprising the CDRs of GC33. One would readily envisage that the antibody of Gonzalez has the same properties of binding GPC3. "The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1997).

17. Claims 10-14, 16 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Pilia et al. (Nature Genetics 12:241-247 (1996); cited in the IDS of 12/10/07).

The interpretation of Claims 10-14, 16 and 33 is discussed above.

Pilia discloses producing rabbit polyclonal antibodies generated against 4 peptide sequences described as having "marked hydrophobic character" and one of which corresponds to residues 533-547 of human GPC3, specifically, DDAPGNSQQATPKDN (p. 247, Col. 1, ¶3). The peptide of Pilia is overlapping in whole or in part with the peptides of Claims 10-14 and 33. It is generally expected that within a heterogeneous population of polyclonal antibodies, some could be found that would bind to a peptide consisting of residues 524-563 or residues 537-563 or residues 550-563 or residues 544 or residues 546-551 of GPC3 or that there would be an antibody which does not bind to a peptide consisting of residues 550-563 of glypican 3. Further within the heterogeneous population of polyclonal antibodies, some could be found that could bind the same epitope as the GC33 antibody or an antibody comprising the CDRs of GC33. One would readily envisage that the antibodies of Pilia could have the same properties of binding GPC3. "The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254,

195 USPQ 430, 433 (CCPA 1997).

18. Claims 3, 7, 9-18 and 33 are rejected under 35 U.S.C. 102(e) as being anticipated by Aburatani et al. (WO/ 2004/022739; published 3/18/04; filed 9/4/02; cited in the IDS of 12/10/07; English language translation equivalent attached as EP 1541680; published 6/15/05; filed 4/9/03).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claims 3 and 7 are drawn to glypican 3 binding Mabs comprising the VH/VL CDRs of the M3B8, M13B3, M6B1, M5B9 and M10D2 (elements (3), (9), (11), (12) and (13) of Claim 3, respectively), and where the antibodies are humanized (Claim 7).

The interpretation of Claims 9-18 and 33 is discussed supra.

Aburatani discloses the anti-glypican 3 Mabs, M3B8, M13B3, M6B1, M5B9 and M10D2, and whose sequences (VH/VL and corresponding CDR regions) are inherent to those of the same Mabs of the instant claims [0142-0144; Figure 9-11]. Aburatani discloses GPC3 Mabs having ADCC and CDC activity (Figures 10-11).

Aburatani discloses humanized forms of these antibodies [0066-0070] and thus a humanized antibody capable of binding to glypican 3, and generating polyclonal or

monoclonal antibodies against C-terminal fragments, for example [0035-0038]. It is generally expected that within a heterogeneous population of polyclonal antibodies, and even amongst a pool of monoclonal antibodies, that some could be found that would bind to a peptide consisting of residues 524-563 or residues 537-563 or residues 550-563 or residues 544 or residues 546-551 of GPC3 or that there would be an antibody which does not bind to a peptide consisting of residues 550-563 of glypican 3. Further within the heterogeneous population of polyclonal antibodies, some could be found that could bind the same epitope as the GC33 antibody or an antibody comprising the CDRs of GC33. One would readily envisage that the antibodies of Aburatani could have the same properties of binding GPC3. "The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1997).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 9-15, 17, 18 and 33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9 and 23-29 of copending Application No. 10/526,741 ("'741"; US 20060167232; filed 9/4/02; cited in the IDS of 12/10/07). Although the conflicting claims are not identical, they are not patentably distinct from each other because Claims 9 and 23-29 of '741 are a species of antibody that read on the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 9 and 15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of copending Application No. 11/414676 ("'676"; US 20060188510; filed 9/4/02) in view of Queen (USPN 5, 530,101; published June 25, 1996).

Although the conflicting claims are not identical, they are not patentably distinct from each other because Claims 1-5 of '676 are a species of antibody that read on the instant claims in view of Queen who teaches the advantages of humanized antibodies.

This is a provisional obviousness-type double patenting rejection.

Conclusion

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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